

## PATENT ABSTRACTS OF JAPAN

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## (54) ACTIVE OXYGEN SCAVENGER AND COMPOSITION CONTAINING THE SAME

## (57)Abstract:

PURPOSE: To obtain the subject highly safe scavenger having activity to sufficiently scavenge active oxygen produced in vivo, and a composition containing this scavenger.

CONSTITUTION: This active oxygen scavenger is an extract from walnutshells. The scavenger is formulated in a composition such as a food or medicine to obtain the objective composition.

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CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE INVENTION TECHNICAL PROBLEM  
MEANS OPERATION EXAMPLE CORRECTION OR AMENDMENT

[Translation done.]

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## CLAIMS

## [Claim(s)]

[Claim 1] The active oxygen elimination agent which consists of an extract of walnut husks.

[Claim 2] The active oxygen elimination agent according to claim 1 characterized by extracting said extract by one sort chosen from water, a methanol, ethanol, n-propyl alcohol, i-propyl alcohol, n-butyl alcohol, i-butyl alcohol, sec-butyl alcohol, t-butyl alcohol, and an acetone, or two sorts or more.

[Claim 3] The constituent containing an active oxygen elimination agent according to claim 1.

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DETAILED DESCRIPTION

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## [Detailed Description of the Invention]

## [0001]

[Industrial Application] This invention relates to the constituent which contains in detail the active oxygen elimination agent which consists of an extract of walnut husks, and this active oxygen elimination agent about the constituent containing an active oxygen elimination agent and this.

## [0002]

[Description of the Prior Art] Generally as effect which active oxygen does to a living body Damage on the organization by bridge formation of a collagen fiber, and the partial cleavage of a DNA spiral and generating of a connective radical is mentioned. Inducement of allergic responses, such as aging of the skins as the result, such as Siwa and elasticity disappearance, or a living body, and bronchial asthma, and inducement of the inflammation by histamine emission. It is known that induction of the dementia by aggravation of diseases, such as damage on the smooth muscle in the myocardial infarction which is one of the ischemic diseases, and a liver failure, and destruction of brain tissue etc. will be caused. Furthermore, although the detailed cause and the device are unknown, they are a fact also with well-known active oxygen also participating also in the onset of rheumatism.

[0003] Therefore, it is very important to control generating of active oxygen in in the living body at the point which treats or prevents these diseases, and, for this reason, retrieval research of the drugs which have the operation which eliminates the active oxygen generated conventionally in the living body has been done widely.

[0004] For example, as what is used conventionally, the tocopherol (vitamin E) of lipophilicity, a water-soluble ascorbic acid (vitamin C), etc. are mentioned by the thing of the natural product origin as drugs which have such an operation, and BHT (3, 5-tert-butyl-4-hydroxytoluene), BHA (2(3)-tert-butyl-hydronalium KISHIANI reel), etc. are mentioned in a synthetic compound. However, about these drugs, there were problems that an active oxygen elimination operation was not enough and — there arises carcinogenic misgiving — by BHT of a synthetic compound, and BHA.

[0005] Moreover, recently, it asks for sufficient drug effect and sufficient safety, and many attempts in which the drugs which have an active oxygen elimination operation will be obtained from a crude drug extract are also made. For example, these all use an active oxygen elimination operation of a crude drug origin object for JP,60-224629,A, JP,61-24522,A, JP,2-193930,A, JP,2-243632,A, JP,2-264727,A, JP,3-153629,A, JP,3-221587,A, JP,4-69343,A, JP,4-202138,A, JP,4-247010,A, etc. However, in these crude drug extracts, although there was no problem in safety, when saying from the point of an active oxygen elimination operation, still sufficient thing was not obtained.

[0006] Furthermore, although the attempt which eliminates the active oxygen generated in the living body by prescribing 1 super oxide DESUMYUTAZE (SOD) of an enzyme for the patient has also been made, since SOD was protein, although the acquisition is not only difficult, but will be digested therefore, internal use was impossible and administration by injection was not that with which the half-life in blood is short and satisfaction goes, either.

[0007] On the other hand, about the husks of a walnut, knowledge with the grinding object useful as a scrub agent and its extract extractives are excellent in moistness as skin external preparations, and useful knowledge is known. However, it was not known that the extract extractives of these walnut husks have an active oxygen elimination operation, and drugs, food, etc. were made to contain this, and the attempt in which it used for various prevention and therapies of a disease which were mentioned above, prevention of aging, and an improvement was not carried out.

## [0008]

[Problem(s) to be Solved by the Invention] This invention makes it a technical problem to offer the constituent which is made from the above-mentioned viewpoint, and has the operation which fully eliminates the active oxygen generated in the living body, and contains an active oxygen elimination agent and this with high safety.

## [0009]

[Means for Solving the Problem] In order that this invention persons may solve the above-mentioned technical problem, while screening various matter by making an active oxygen elimination operation into an index That the fruit of the walnut which contains inside husks the partial saturation fats and oils which are easy to receive degradation by active oxygen can maintain internal partial saturation fats and oils at stability When it reasoned that it was because the defense mechanism over a certain active oxygen exists in outer husks and the walnut husks extract was covered over screening of an active oxygen elimination agent, it came to complete a header and this invention for the component which has the active oxygen elimination operation excellent in this walnut husks extract component existing.

[0010] That is, this invention relates to the constituent containing the active oxygen elimination agent and this which consist of an extract of walnut husks. Hereafter, this invention is explained to a detail.

[0011] The active oxygen elimination agent of active oxygen elimination agent this invention of <1> this invention consists of an extract of walnut husks. The walnut husks used for this invention are husks of the fruits of the Juglandaceae vegetation generally known, for example, walnut husks, such as demon GURUMI, MANSHUUGURUMI, and the Wall nuts, are mentioned.

[0012] The above-mentioned walnut husks take out the extract which contains the component which has an active oxygen elimination operation, and contains said component by extract, and it is used for them as an active oxygen elimination agent of this invention. Extract processings of walnut husks are approaches, such as continuous system and a batch type, and are performed the time of arbitration by maceration or digestion with a conventional method. For example, walnut husks are pulverized finely and it extracts by being immersed by one - three days, or the boiling temperature of an extracting solvent at a room temperature to an extracting solvent for 1 hour to 5 hours. Then, except for extract residue, reduced pressure or an ultrafiltration is performed from an extract, and an extract is condensed. or [ furthermore, / distilling off an organic solvent completely and hardening by drying if needed. ] — or it freeze-dries.

[0013] As a solvent used for such an extract, although water and various organic solvents are mentioned, one sort chosen from

water, a methanol, ethanol, n-propyl alcohol, i-propyl alcohol, n-butyl alcohol, i-butyl alcohol, sec-butyl alcohol, t-butyl alcohol, and an acetone especially in this invention or two sorts or more are desirable.

[0014] The constituent of constituent this invention containing the active oxygen elimination agent of <2> this inventions blends the above-mentioned active oxygen elimination agent according to a conventional method, for example, drugs, food, etc. are mentioned.

[0015] Although especially a pharmaceutical form is not limited when pharmaceutical-preparation-izing it, using the active oxygen elimination agent of this invention as drugs, according to the usual approach,-izing can be carried out [ pharmaceutical form ] with the arbitration component usually used by drugs, such as an excipient, a binder, disintegrator, lubricant, a coloring agent, corrigent, an odor-masking agent, an extending agent, and coating, to various pharmaceutical preparation usually used, such as injections, powder, a granule, a tablet, a capsule, and liquids and solutions.

[0016] although it changes with the class of disease, a symptom, a patient's age, weights, etc. about the dose of the above-mentioned drugs — an adult — it is appropriate for one person to administer 10mg ~ 1000mg orally in 1 time thru/or several steps as an amount of the extract of per day and walnut husks, or to prescribe 5mg ~ 500mg for the patient by injection. As a medication method of injections, intravenous administration, intraarterial administration, the administration in a portal vein, intraperitoneal administration, intramuscular administration, subcutaneous administration, etc. are mentioned.

[0017] It can blend with various food with the arbitration component usually used with food, without minding especially, when blending the active oxygen elimination agent of this invention with food. If it illustrates, the staple food, such as confectionary, such as a candy, and GUMI and jelly, drinks like juice, and a pan, etc. will be mentioned. Although loadings change with classes of food, in order to acquire sufficient active oxygen elimination effectiveness, without spoiling the taste of food, its 0.1 ~ 10 % of the weight is desirable.

[0018] In addition, since walnuts are edible fruits, the extract of walnut husks can expect to excel in safety.

[0019]

[Function] The constituent containing the active oxygen elimination agent of this invention and this work effectively to the improvement of living body aging, such as a therapy of various illnesses, such as ischemic diseases, such as the inflammation and the senile dementia it be suppose that active oxygen be involve according to the active oxygen elimination operation which be excellent in the walnut husks extract which be the active principle as mention above, and myocardial infarction, or an allergic disease, a liver failure, and rheumatism, and the skin.

[0020] Moreover, the constituent containing the active oxygen elimination agent of this invention and this can be used effectively also because of prevention of the above-mentioned illness or living body aging. This is because the active oxygen which generated the component which has an active oxygen elimination operation by making it exist beforehand in the living body in the living body can be eliminated quickly and can be detoxified.

[0021]

[Example] Below, the example of this invention is explained. First, the example of the active oxygen elimination agent of this invention is explained.

[0022]

[Example 1] After having pulverized finely 500g of walnut husks of demon GURUMI, adding 5L water to this and carrying out heating churning at 105 degrees C for 2 hours, it freeze-dried having filtered, having removed residue and having covered 2 \*\*\*s of obtained filtrate, and the walnut husks extract of demon GURUMI was obtained as 4.9g brown powder. This was made into the active oxygen elimination agent as it was.

[0023]

[Example 2] After having pulverized 500g of walnut husks of MANSHUUGURUMI finely, adding 5L of equivalent mixed liquor of a methanol and n-butyl alcohol to this and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed, vacuum concentration of the obtained filtrate was carried out, and 5.3g was obtained for the walnut husks extract of MANSHUUGURUMI as a viscosity nature liquid. This was made into the active oxygen elimination agent as it was.

[0024]

[Example 3] After having pulverized finely 500g of walnut husks of the Wall nuts, adding 5L of acetone water solutions to this 50% and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed and vacuum concentration of the obtained filtrate was carried out. Furthermore, freeze-drying processing of this concentrate was carried out over 48 hours, and the walnut husks extract of the Wall nuts was obtained as 5.1g being amorphous. This was made into the active oxygen elimination agent as it was.

[0025] About the active oxygen elimination agent obtained in <evaluation of active oxygen elimination agent> above-mentioned each example, evaluation about safety, an active oxygen elimination operation and aging, a liver failure, and the effectiveness over the allergosis was performed.

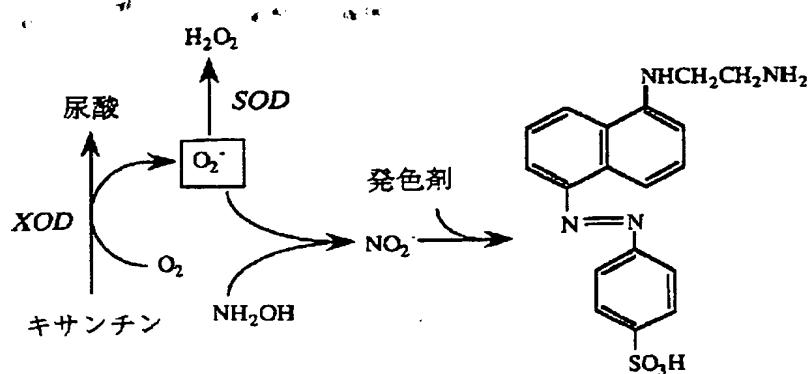
[0026] (1) Intraperitoneal [ of the 5 weeks old ICR male mouse (weights 25~30g) of every two acute toxicity test 1 groups ] was medicated with what dissolved the active oxygen elimination agent obtained in the example 1 in the physiological saline at a rate of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg, respectively, and life and death were judged 14 days after. Consequently, the mouse survived also in said which dose and it was checked that a fifty percent lethal dose value is 2000mg/kg or more. It is clear that the active oxygen elimination agent of this invention excels this in safety.

[0027] (2) Measurement of an active oxygen elimination operation (in vitro)

Based on the reaction formula shown in \*\* 1, the yield of O<sub>2</sub>· which was made to generate the superoxide anion (O<sub>2</sub>·) which is one of the active oxygen by the xanthin-xanthine oxidase (XOD) system, and was generated was measured by the nitrous-acid method, this value was amended with the xanthine oxidase inhibition activity value, and the active oxygen elimination operation value was calculated.

[0028]

[Formula 1]



[0029] 0.1ml of active oxygen elimination agent water solutions which contain the active oxygen elimination agent obtained in each above-mentioned example at a 500microg [/ml] rate could be added to 65mM potassium dihydrogen phosphate, 35mM sodium borate, 0.2ml (henceforth the buffer solution A) of 0.5mMEDTA disodium water solutions, 0.2ml of 0.5mM xanthin solutions, 0.1ml of 10mM hydroxylamine-hydrochloride water solutions, and the mixed liquor of 0.2ml of pure water, they were agitated, and were used as test fluid. Similarly, the solution of the control which used 0.1ml of pure water instead of the active oxygen elimination agent was produced.

[0030] After adding 0.2ml of buffer solutions A which contain xanthine oxidase by 1microl. [/ml] concentration and agitating them in each above-mentioned test fluid and a control solution, the incubation was carried out at 37 degrees C for 30 minutes. 0.2ml of buffer solutions A which do not contain xanthine oxidase in the test fluid and the control solution which were adjusted like the above as a blank was added, and the solution processed like the above was prepared.

[0031] Thus, after adding a 30microMN-1-naphthyl ethylenediamine hydrochloride, 3mM sulfanilic acid, and 2ml of 25% glacial-acetic-acid mixtures to each of each obtained solution and leaving it at a room temperature for 30 minutes, about each solution, the yield of active oxygen was measured with the absorbance in 550nm, and the yield of a uric acid was measured with the absorbance of 295nm.

[0032] Based on the following formulas, the active oxygen elimination activity value was computed using the acquired value. A result is shown in Table 2.

[0033] < active oxygen elimination activity Formula > active oxygen incidence-rate =[for which it asks The notation in (A550-3-A550-4) / (A550-1-A550-2)]x100 uric-acid yield =[(A295-3-A295-4)/(A295-1-A295-2)] x100 active-oxygen elimination activity =100-(active oxygen incidence-rate / uric-acid yield) x100, however a formula It considers as the value of the absorbance of each solution adjusted on the conditions shown in Table 1.

[0034]

[Table 1]

測定波長 (nm)		キサンチンオキシダーゼ	
		存在下	非存在下
550 (活性酸素量)	コントロール 試験液	A <sub>550-1</sub> A <sub>550-3</sub>	A <sub>550-2</sub> A <sub>660-4</sub>
295 (尿酸量)	コントロール 試験液	A <sub>295-1</sub> A <sub>295-3</sub>	A <sub>295-2</sub> A <sub>295-4</sub>

[0035]

[Table 2]

	活性酸素消去活性値 (%)
実施例 1 の活性酸素消去剤	67.1
実施例 2 の活性酸素消去剤	66.2
実施例 3 の活性酸素消去剤	67.5

It is clear from the above result that the active oxygen elimination agent of this invention has the outstanding active oxygen elimination operation.

[0036] (3) Measurement of an active oxygen elimination operation (in vivo)

After performing blood collecting from a 35-weeks old ICR system MCH male mouse (weights 30-40g), the active oxygen elimination agent obtained in the example 1 was administered orally to this mouse at a rate of 1000 mg/kg. It collected blood after [ of administration ] 30 minutes, and 2 hours and 5 hours after. The blood serum was picked out from the blood which collected blood with the above-mentioned monograph affair according to centrifugal separation, this was diluted with the buffer

solution A 10 times, and active oxygen elimination activity was measured by the same approach as the trial of the above (2). A result is shown in Table 3.

[0037]

[Table 3]

	活性酸素消去活性値 (%)
投与前	47.8 ± 15.4
投与30分後	62.9 ± 10.9
2時間後	49.6 ± 7.6
5時間後	58.4 ± 4.5

It is clear for the active oxygen elimination agent of this invention to shift into blood promptly by internal use, and to maintain that effectiveness from this result, for a long time.

[0038] (4) 40 5 weeks old Wister system femininity rats of examination of the effectiveness over aging and a hepatopathy were divided into the appearance which does not have dispersion in weight at four groups, said pellet was made to take in the usual pellet (F2 feed, made in the Funabashi farm) in other three groups, and the active oxygen elimination agent of each example was bred [ at one group / the pellet ] for 1% of the weight of the blended thing for 24 months to it, respectively. In addition, it enabled it to take in a pellet and water freely to a rat during an experiment.

[0039] After 24-month breeding, it slaughtered, after extracting blood from the rat of each group. Then, the existence of an appearance was observed about disappearance of disseminated depilation, the plumping plasmotomy of the connective tissue under epidermis, sebaceous gland, and a sudoriferous gland as an evaluation index of aging about the rat of each group.

[0040] Furthermore, these rats were dissected, liver was extracted and evaluation about a hepatopathy was performed by observing under a microscope as an upper pathology sample of macroscopic observation. Moreover, although it reacted easily with unsaturated fatty acid in the living body and peroxylipid was produced when active oxygen occurred in the living body, the active oxygen elimination effectiveness in each organ was evaluated by measuring the amount of peroxylipid which carried out in this way and was produced to each part of the inside of the body (inside of a blood serum, a brain, and liver) by the TBA method.

[0041] A result is shown [ amount / of peroxylipid ] in Table 4 as the number of appearance animals about other evaluation criteria as the average of ten animals.

[0042]

[Table 4]

		実施例 1	実施例 2	実施例 3	コントロール
過酸化脂質量	血清中	11	10	10	18
	脳中	24	25	23	27
	肝臓中	29	29	27	36
<老化の評価>					
散在性脱毛		0	0	0	3
表皮下の結合組織の膨化断裂		0	0	0	4
脂腺、汗腺の消失		0	0	0	2
<肝障害の評価>					
肝臓への脂肪沈着		0	0	0	6
肝臓小葉への炎症細胞の浸潤		0	0	0	4
萎縮肝細胞		0	0	0	2

In each organ in the living body, it is clear the active oxygen elimination agent's of this invention to have controlled generation of peroxylipid well by eliminating active oxygen, and to have prevented a living body's aging, and to have prevented the failure of liver.

[0043] (5) According to the guinea pig maximization test method of examination KURIGUMAN of effectiveness to the allergosis, evaluation to an allergic induction reaction was performed using the cinnamaldehyde which is the sensitizer.

[0044] The following experiments were conducted having made said pellet take in freely 1% of the weight of the thing and water which were blended for the active oxygen elimination agent of each example in other three groups, and breeding a usual pellet (F2 feed, made in the Funabashi farm) and water in them at two groups (among these, one group control group) of the guinea pig of every one groups [ 8-10 ], respectively.

[0045] Intradermal injection of 4 times, 1% cinnamaldehyde liquid paraffin solution, the equivalent mixed liquor of Freund's complete adjuvant, 1% cinnamaldehyde liquid paraffin solution, and the 0.05ml of the Freund's complete adjuvant was carried out to the guinea pig of each above-mentioned group except the guinea pig of a control group every two days at every two places of

every regions of back. Furthermore, from the injection opening day, the closed patch of what applied the cinnamaldehyde liquid paraffin solution to the putt section of an adhesive bandage 1% was carried out, and dermal administration was also performed at least in the period by the injection end date, and the above-mentioned injection section at coincidence.

[0046] The regions of back of all guinea pigs were shaved after two weeks, injection and a closed patch end date, dermal administration of each cinnamaldehyde liquid paraffin solution of 0.01%, 0.05%, 0.1%, 0.5%, and 1% concentration was carried out by the approach of carrying out a closed patch like the above for 24 hours, and the induction reaction was seen. The Japanese Dermatological Association this country patch test criteria shown below were used for the criteria of evaluation. A result is shown in Table 5.

[0047] - : Adiaphorous \*\* : False positive reaction + : Positive reaction ++ : Reaction accompanied by an edema [0048]

[Table 5]

		実施例 1	実施例 2	実施例 3	通常飼料	コントロール群
0. 01%	-	4/8	4/10	5/9	3/10	9/9
	±	4/8	6/10	4/9	4/10	0/9
	+	0/8	0/10	0/9	3/10	0/9
	++	0/8	0/10	0/9	0/10	0/9
0. 05%	-	4/8	4/10	5/9	2/10	9/9
	±	4/8	6/10	4/9	3/10	0/9
	+	0/8	0/10	0/9	5/10	0/9
	++	0/8	0/10	0/9	0/10	0/9
0. 1%	-	2/8	2/10	3/9	0/10	9/9
	±	4/8	5/10	6/9	4/10	0/9
	+	2/8	3/10	0/9	5/10	0/9
	++	0/8	0/10	0/9	1/10	0/9
0. 5%	-	0/8	0/10	0/9	0/10	9/9
	±	5/8	6/10	8/9	3/10	0/9
	+	3/8	4/10	0/9	5/10	0/9
	++	0/8	0/10	1/9	2/10	0/9
1%	-	0/8	0/10	0/9	0/10	5/9
	±	4/8	5/10	7/9	0/10	4/9
	+	4/8	4/10	1/9	5/10	0/9
	++	0/8	1/10	1/9	5/10	0/9

The active oxygen elimination agent of this invention has controlled the good allergic induction reaction so that clearly from this result.

[0049] Next, the example of constituents, such as food, drugs, etc. containing the active oxygen elimination agent obtained in the above-mentioned example, is explained. In addition, especially all the things in which the loadings used for below do not have a notice are the weight sections.

[0050]

[Examples 4-6] The heating dissolution of the A component was carried out at 150 degrees C among the candy table 6, after casting what made B component homogeneity after addition and churning, it cooled and the candy was manufactured [ after cooling at 120 degrees C ].

[0051]

[Table 6]

成 分		配 合 量		
		実施例 4	実施例 5	実施例 6
A	砂 糖 水 餡	58.0 30.0	67.0 30.0	67.0 30.9
B	クエン酸 実施例 1 の活性酸素消去剤 実施例 2 の活性酸素消去剤 実施例 3 の活性酸素消去剤 香 料	1.0 10.0 — — 1.0	1.0 — 1.0 — 1.0	1.0 — — 0.1 1.0

[0052]

[Example 7] B component which the heating dissolution was carried out [ component ] and carried out the swelling dissolution of the A component of the GUMI table 7 separately at 110 degrees C was added, further, C component was added and it slushed into the mold, and after neglect, it removed from the mold and GUMI was manufactured one whole day and night.

[0053]

[Table 7]

成 分		配 合 量
A	砂 糖 水 餡	40.0 45.0
B	ゼラチン	8.0
C	クエン酸 実施例 3 の活性酸素消去剤 香 料	2.0 4.0 1.0

[0054]

[Example 8] the component of the juice table 8 — good — agitating — a solution — carrying out — sterilization and aseptic — it sealed and juice was manufactured.

[0055]

[Table 8]

成 分		配 合 量
リンゴ果汁 実施例 1 の活性酸素消去剤		98.0 2.0

[0056]

[Example 9] The component of the hot cake table 9 was often mixed, it roasted with the frying pan which oiled, and the hot cake was created.

[0057]

[Table 9]

成 分	配 合 量
ホットケーキミックス（市販）	240 g
牛 乳	180 ml
全 卵	2 個
実施例 2 の活性酸素消去剤	5 g

[0058]

[Example 10] A component of the granule table 10 was often mixed, and in addition, it corned gradually, carrying out kneading of the B component melted in the ethanol water solution 20 100ml% at this. this — 40 degrees C — 2 day-and-night ventilation desiccation — carrying out — screening — the particle size regulation was carried out and it considered as the granule.

[0059]

[Table 10]

成 分		配 合 量
A	乳 糖	4 5
	デキストラン	4 5
	実施例 1 の活性酸素消去剤	5
B	ヒドロキシプロピルセルロース	5

[0060]

[Example 11] The component of the injections table 11 was dissolved, and it filtered, and sterilized, and into ampul, aseptic was carried out, and it enclosed, and considered as injections.

[0061]

[Table 11]

成 分		配 合 量
塩化ナトリウム		0. 9
実施例 3 の活性酸素消去剤		0. 1
精 製 水		99. 0

[0062]

[Effect of the Invention] Its safety is high, and since the constituent containing the active oxygen elimination agent of this invention and this has the outstanding active oxygen elimination operation, it is effective in prevention of the allergosis in which active oxygen participates, and a hepatopathy, and prevention of a therapy and living body aging.

[Translation done.]

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TECHNICAL FIELD

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## PRIOR ART

[Description of the Prior Art] Generally as effect which active oxygen does to a living body Damage on the organization by bridge formation of a collagen fiber, and the partial cleavage of a DNA spiral and generating of a connective radical is mentioned. Inducement of allergic responses, such as aging of the skins as the result, such as Siwa and elasticity disappearance, or a living body, and bronchial asthma, and inducement of the inflammation by histamine emission, It is known that induction of the dementia by aggravation of diseases, such as damage on the smooth muscle in the myocardial infarction which is one of the ischemic diseases, and a liver failure, and destruction of brain tissue etc. will be caused. Furthermore, although the detailed cause and the device are unknown, they are a fact also with well-known active oxygen also participating also in the onset of rheumatism.

[0003] Therefore, it is very important to control generating of active oxygen in the living body at the point which treats or prevents these diseases, and, for this reason, retrieval research of the drugs which have the operation which eliminates the active oxygen generated conventionally in the living body has been done widely.

[0004] For example, as what is used conventionally, the tocopherol (vitamin E) of lipophilicity, a water-soluble ascorbic acid (vitamin C), etc. are mentioned by the thing of the natural product origin as drugs which have such an operation, and BHT (3, 5-tert-butyl-4-hydroxytoluene), BHA (2(3)-tert-butyl-hydronalum KISHIANI reel), etc. are mentioned in a synthetic compound. However, about these drugs, there were problems that an active oxygen elimination operation was not enough and --- there arises carcinogenic misgiving --- by BHT of a synthetic compound, and BHA.

[0005] Moreover, recently, it asks for sufficient drug effect and sufficient safety, and many attempts in which the drugs which have an active oxygen elimination operation will be obtained from a crude drug extract are also made. For example, these all use an active oxygen elimination operation of a crude drug origin object for JP,60-224629,A, JP,61-24522,A, JP,2-193930,A, JP,2-243632,A, JP,2-264727,A, JP,3-153629,A, JP,3-221587,A, JP,4-69343,A, JP,4-202138,A, JP,4-247010,A, etc. However, in these crude drug extracts, although there was no problem in safety, when saying from the point of an active oxygen elimination operation, still sufficient thing was not obtained.

[0006] Furthermore, although the attempt which eliminates the active oxygen generated in the living body by prescribing 1 super oxide DESUMYUTAZE (SOD) of an enzyme for the patient has also been made, since SOD was protein, although the acquisition is not only difficult, but will be digested therefore, internal use was impossible and administration by injection was not that with which the half-life in blood is short and satisfaction goes, either.

[0007] On the other hand, about the husks of a walnut, knowledge with the grinding object useful as a scrub agent and its extract extractives are excellent in moistness as skin external preparations, and useful knowledge is known. However, it was not known that the extract extractives of these walnut husks have an active oxygen elimination operation, and drugs, food, etc. were made to contain this, and the attempt in which it used for various prevention and therapies of a disease which were mentioned above, prevention of aging, and an improvement was not carried out.

[Translation done.]

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**EFFECT OF THE INVENTION**

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[Effect of the Invention] Its safety is high, and since the constituent containing the active oxygen elimination agent of this invention and this has the outstanding active oxygen elimination operation, it is effective in prevention of the allergosis in which active oxygen participates, and a hepatopathy, and prevention of a therapy and living body aging.

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TECHNICAL PROBLEM

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[Problem(s) to be Solved by the Invention] This invention makes it a technical problem to offer the constituent which is made from the above-mentioned viewpoint, and has the operation which fully eliminates the active oxygen generated in the living body, and contains an active oxygen elimination agent and this with high safety.

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## MEANS

[Means for Solving the Problem] In order that this invention persons may solve the above-mentioned technical problem, while screening various matter by making an active oxygen elimination operation into an index That the fruit of the walnut which contains inside husks the partial saturation fats and oils which are easy to receive degradation by active oxygen can maintain internal partial saturation fats and oils at stability When it reasoned that it was because the defense mechanism over a certain active oxygen exists in outer husks and the walnut husks extract was covered over screening of an active oxygen elimination agent, it came to complete a header and this invention for the component which has the active oxygen elimination operation excellent in this walnut husks extract component existing.

[0010] That is, this invention relates to the constituent containing the active oxygen elimination agent and this which consist of an extract of walnut husks. Hereafter, this invention is explained to a detail.

[0011] The active oxygen elimination agent of active oxygen elimination agent this invention of <1> this invention consists of an extract of walnut husks. The walnut husks used for this invention are husks of the fruits of the Juglandaceae vegetation generally known, for example, walnut husks, such as demon GURUMI, MANSHUUGURUMI, and the Wall nuts, are mentioned.

[0012] The above-mentioned walnut husks take out the extract which contains the component which has an active oxygen elimination operation, and contains said component by extract, and it is used for them as an active oxygen elimination agent of this invention. Extract processings of walnut husks are approaches, such as continuous system and a batch type, and are performed the time of arbitration by maceration or digestion with a conventional method. For example, walnut husks are pulverized finely and it extracts by being immersed by one - three days, or the boiling temperature of an extracting solvent at a room temperature to an extracting solvent for 1 hour to 5 hours. Then, except for extract residue, reduced pressure or an ultrafiltration is performed from an extract, and an extract is condensed. or [ furthermore, / distilling off an organic solvent completely and hardening by drying if needed. ] — or it freeze-dries.

[0013] As a solvent used for such an extract, although water and various organic solvents are mentioned, one sort chosen from water, a methanol, ethanol, n-propyl alcohol, i-propyl alcohol, n-butyl alcohol, i-butyl alcohol, sec-butyl alcohol, t-butyl alcohol, and an acetone especially in this invention or two sorts or more are desirable.

[0014] The constituent of constituent this invention containing the active oxygen elimination agent of <2> this inventions blends the above-mentioned active oxygen elimination agent according to a conventional method, for example, drugs, food, etc. are mentioned.

[0015] Although especially a pharmaceutical form is not limited when pharmaceutical-preparation-izing it, using the active oxygen elimination agent of this invention as drugs, according to the usual approach,-izing can be carried out [ pharmaceutical form ] with the arbitration component usually used by drugs, such as an excipient, a binder, disintegrator, lubricant, a coloring agent, corrigent, an odor-masking agent, an extending agent, and coating, to various pharmaceutical preparation usually used, such as injections, powder, a granule, a tablet, a capsule, and liquids and solutions.

[0016] although it changes with the class of disease, a symptom, a patient's age, weights, etc. about the dose of the above-mentioned drugs — an adult — it is appropriate for one person to administer 10mg - 1000mg orally in 1 time thru/or several steps as an amount of the extract of per day and walnut husks, or to prescribe 5mg - 500mg for the patient by injection. As a medication method of injections, intravenous administration, intraarterial administration, the administration in a portal vein, intraperitoneal administration, intramuscular administration, subcutaneous administration, etc. are mentioned.

[0017] It can blend with various food with the arbitration component usually used with food, without minding especially, when blending the active oxygen elimination agent of this invention with food. If it illustrates, the staple food, such as confectionary, such as a candy, and GUMI and jelly, drinks like juice, and a pan, etc. will be mentioned. Although loadings change with classes of food, in order to acquire sufficient active oxygen elimination effectiveness, without spoiling the taste of food, its 0.1 - 10 % of the weight is desirable.

[0018] In addition, since walnuts are edible fruits, the extract of walnut husks can expect to excel in safety.

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OPERATION

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[Function] The constituent containing the active oxygen elimination agent of this invention and this work effectively to the improvement of living body aging , such as a therapy of various illnesses , such as ischemic diseases , such as the inflammation and the senile dementia it be suppose that active oxygen be involve according to the active oxygen elimination operation which be excellent in the walnut husks extract which be the active principle as mention above , and myocardial infarction , or an allergic disease , a liver failure , and rheumatism , and the skin .

[0020] Moreover, the constituent containing the active oxygen elimination agent of this invention and this can be used effectively also because of prevention of the above-mentioned illness or living body aging. This is because the active oxygen which generated the component which has an active oxygen elimination operation by making it exist beforehand in the living body in the living body can be eliminated quickly and can be detoxified.

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## EXAMPLE

[Example] Below, the example of this invention is explained. First, the example of the active oxygen elimination agent of this invention is explained.

[0022]

[Example 1] After having pulverized finely 500g of walnut husks of demon GURUMI, adding 5l. water to this and carrying out heating churning at 105 degrees C for 2 hours, it freeze-dried having filtered, having removed residue and having covered 2 \*\*\*\*s of obtained filtrate, and the walnut husks extract of demon GURUMI was obtained as 4.9g brown powder. This was made into the active oxygen elimination agent as it was.

[0023]

[Example 2] After having pulverized 500g of walnut husks of MANSHUUGURUMI finely, adding 5l. of equivalent mixed liquor of a methanol and n-butyl alcohol to this and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed, vacuum concentration of the obtained filtrate was carried out, and 5.3g was obtained for the walnut husks extract of MANSHUUGURUMI as a viscosity nature liquid. This was made into the active oxygen elimination agent as it was.

[0024]

[Example 3] After having pulverized finely 500g of walnut husks of the Wall nuts, adding 5l. of acetone water solutions to this 50% and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed and vacuum concentration of the obtained filtrate was carried out. Furthermore, freeze-drying processing of this concentrate was carried out over 48 hours, and the walnut husks extract of the Wall nuts was obtained as 5.1g being amorphous. This was made into the active oxygen elimination agent as it was.

[0025] About the active oxygen elimination agent obtained in <evaluation of active oxygen elimination agent> above-mentioned each example, evaluation about safety, an active oxygen elimination operation and aging, a liver failure, and the effectiveness over the allergosis was performed.

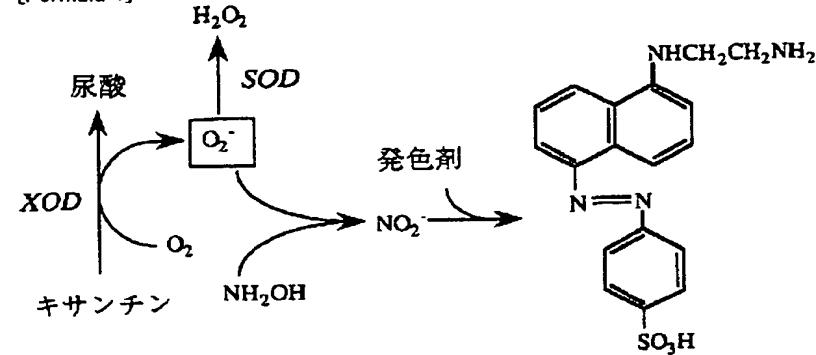
[0026] (1) Intraperitoneal [ of the 5 weeks old ICR male mouse (weights 25-30g) of every two acute toxicity test 1 groups ] was medicated with what dissolved the active oxygen elimination agent obtained in the example 1 in the physiological saline at a rate of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg, respectively, and life and death were judged 14 days after. Consequently, the mouse survived also in said which dose and it was checked that a fifty percent lethal dose value is 2000mg/kg or more. It is clear that the active oxygen elimination agent of this invention excels this in safety.

[0027] (2) Measurement of an active oxygen elimination operation (in vitro)

Based on the reaction formula shown in \*\* 1, the yield of O<sub>2</sub><sup>-</sup> which was made to generate the superoxide anion (O<sub>2</sub><sup>-</sup>) which is one of the active oxygen by the xanthin-xanthine oxidase (XOD) system, and was generated was measured by the nitrous-acid method, this value was amended with the xanthine oxidase inhibition activity value, and the active oxygen elimination operation value was calculated.

[0028]

[Formula 1]



[0029] 0.1ml of active oxygen elimination agent water solutions which contain the active oxygen elimination agent obtained in each above-mentioned example at a 500microg [/ml] rate could be added to 65mM potassium dihydrogen phosphate, 35mM sodium borate, 0.2ml (henceforth the buffer solution A) of 0.5mMEDTA disodium water solutions, 0.2ml of 0.5mM xanthin solutions, 0.1ml of 10mM hydroxylamine-hydrochloride water solutions, and the mixed liquor of 0.2ml of pure water, they were agitated, and were used as test fluid. Similarly, the solution of the control which used 0.1ml of pure water instead of the active oxygen elimination agent was produced.

[0030] After adding 0.2ml of buffer solutions A which contain xanthine oxidase by 1microl. [/ml] concentration and agitating them in each above-mentioned test fluid and a control solution, the incubation was carried out at 37 degrees C for 30 minutes. 0.2ml of buffer solutions A which do not contain xanthine oxidase in the test fluid and the control solution which were adjusted like the above as a blank was added, and the solution processed like the above was prepared.

[0031] Thus, after adding a 30microMN-1-naphthyl ethylenediamine hydrochloride, 3mM sulfanilic acid, and 2ml of 25% glacial-acetic-acid mixtures to each of each obtained solution and leaving it at a room temperature for 30 minutes, about each solution, the yield of active oxygen was measured with the absorbance in 550nm, and the yield of a uric acid was measured with the absorbance of 295nm.

[0032] Based on the following formulas, the active oxygen elimination activity value was computed using the acquired value. A result is shown in Table 2.

[0033] < active oxygen elimination activity Formula > active oxygen incidence-rate =[for which it asks The notation in (A550-3-A550-4) / (A550-1-A550-2)]x100 uric-acid yield =[(A295-3-A295-4)/(A295-1-A295-2)] x100 active-oxygen elimination activity =100-(active oxygen incidence-rate / uric-acid yield) x100, however a formula it considers as the value of the absorbance of each solution adjusted on the conditions shown in Table 1.

[0034]

[Table 1]

測定波長 (nm)		キサンチンオキシダーゼ	
		存在下	非存在下
550 (活性酸素量)	コントロール 試験液	A <sub>550-1</sub> A <sub>550-3</sub>	A <sub>550-2</sub> A <sub>550-4</sub>
295 (尿酸量)	コントロール 試験液	A <sub>295-1</sub> A <sub>295-3</sub>	A <sub>295-2</sub> A <sub>295-4</sub>

[0035]

[Table 2]

	活性酸素消去活性値 (%)
実施例 1 の活性酸素消去剤	67.1
実施例 2 の活性酸素消去剤	66.2
実施例 3 の活性酸素消去剤	67.5

It is clear from the above result that the active oxygen elimination agent of this invention has the outstanding active oxygen elimination operation.

[0036] (3) Measurement of an active oxygen elimination operation (in vivo)

After performing blood collecting from a 35-weeks old ICR system MCH male mouse (weights 30-40g), the active oxygen elimination agent obtained in the example 1 was administered orally to this mouse at a rate of 1000 mg/kg. It collected blood after [ of administration ] 30 minutes, and 2 hours and 5 hours after. The blood serum was picked out from the blood which collected blood with the above-mentioned monograph affair according to centrifugal separation, this was diluted with the buffer solution A 10 times, and active oxygen elimination activity was measured by the same approach as the trial of the above (2). A result is shown in Table 3.

[0037]

[Table 3]

	活性酸素消去活性値 (%)
投与前	47.8 ± 15.4
投与30分後	62.9 ± 10.9
2時間後	49.6 ± 7.6
5時間後	58.4 ± 4.5

It is clear for the active oxygen elimination agent of this invention to shift into blood promptly by internal use, and to maintain that effectiveness from this result, for a long time.

[0038] (4) 40 5 weeks old Wister system femininity rats of examination of the effectiveness over aging and a hepatopathy were divided into the appearance which does not have dispersion in weight at four groups, said pellet was made to take in the usual pellet (F2 feed, made in the Funabashi farm) in other three groups, and the active oxygen elimination agent of each example was bred [ at one group / the pellet ] for 1% of the weight of the blended thing for 24 months to it, respectively. In addition, it enabled it to take in a pellet and water freely to a rat during an experiment.

[0039] After 24-month breeding, it slaughtered, after extracting blood from the rat of each group. Then, the existence of an appearance was observed about disappearance of disseminated depilation, the plumping plasmotomy of the connective tissue under epidermis, sebaceous gland, and a sudoriferous gland as an evaluation index of aging about the rat of each group.

[0040] Furthermore, these rats were dissected, liver was extracted and evaluation about a hepatopathy was performed by observing under a microscope as an upper pathology sample of macroscopic observation. Moreover, although it reacted easily with unsaturated fatty acid in the living body and peroxylipid was produced when active oxygen occurred in the living body, the

active oxygen elimination effectiveness in each organ was evaluated by measuring the amount of peroxylipid which carried out in this way and was produced to each part of the inside of the body (inside of a blood serum, a brain, and liver) by the TBA method.

[0041] A result is shown [ amount / of peroxylipid ] in Table 4 as the number of appearance animals about other evaluation criteria as the average of ten animals.

[0042]

[Table 4]

		実施例 1	実施例 2	実施例 3	コントロール
過酸化脂質量	血清中	11	10	10	18
	脳中	24	25	23	27
	肝臓中	29	29	27	36
<老化の評価>					
散在性脱毛		0	0	0	3
表皮下の結合組織の膨化断裂		0	0	0	4
脂腺、汗腺の消失		0	0	0	2
<肝障害の評価>					
肝臓への脂肪沈着		0	0	0	6
肝臓小葉への炎症細胞の浸潤		0	0	0	4
萎縮肝細胞		0	0	0	2

In each organ in the living body, it is clear the active oxygen elimination agent's of this invention to have controlled generation of peroxylipid well by eliminating active oxygen, and to have prevented a living body's aging, and to have prevented the failure of liver.

[0043] (5) According to the guinea pig maximization test method of examination KURIGUMAN of effectiveness to the allergosis, evaluation to an allergic induction reaction was performed using the cinnamaldehyde which is the sensitizer.

[0044] The following experiments were conducted having made said pellet take in freely 1% of the weight of the thing and water which were blended for the active oxygen elimination agent of each example in other three groups, and breeding a usual pellet (F2 feed, made in the Funabashi farm) and water in them at two groups (among these, one group control group) of the guinea pig of every one groups [ 8-10 ], respectively.

[0045] Intradermal injection of 4 times, 1% cinnamaldehyde liquid paraffin solution, the equivalent mixed liquor of Freund's complete adjuvant, 1% cinnamaldehyde liquid paraffin solution, and the 0.05ml of the Freund's complete adjuvant was carried out to the guinea pig of each above-mentioned group except the guinea pig of a control group every two days at every two places of every regions of back. Furthermore, from the injection opening day, the closed patch of what applied the cinnamaldehyde liquid paraffin solution to the putt section of an adhesive bandage 1% was carried out, and dermal administration was also performed at least in the period by the injection end date, and the above-mentioned injection section at coincidence.

[0046] The regions of back of all guinea pigs were shaved after two weeks, injection and a closed patch end date, dermal administration of each cinnamaldehyde liquid paraffin solution of 0.01%, 0.05%, 0.1%, 0.5%, and 1% concentration was carried out by the approach of carrying out a closed patch like the above for 24 hours, and the induction reaction was seen. The Japanese Dermatological Association this country patch test criteria shown below were used for the criteria of evaluation. A result is shown in Table 5.

[0047] - : Adiaphorous \*\* : False positive reaction + : Positive reaction ++ : Reaction accompanied by an edema [0048]

[Table 5]

		実施例 1	実施例 2	実施例 3	通常飼料	コントロール群
0. 01%	-	4/8	4/10	5/9	3/10	9/9
	±	4/8	6/10	4/9	4/10	0/9
	+	0/8	0/10	0/9	3/10	0/9
	++	0/8	0/10	0/9	0/10	0/9
0. 05%	-	4/8	4/10	5/9	2/10	9/9
	±	4/8	6/10	4/9	3/10	0/9
	+	0/8	0/10	0/9	5/10	0/9
	++	0/8	0/10	0/9	0/10	0/9
0. 1%	-	2/8	2/10	3/9	0/10	9/9
	±	4/8	5/10	6/9	4/10	0/9
	+	2/8	3/10	0/9	5/10	0/9
	++	0/8	0/10	0/9	1/10	0/9
0. 5%	-	0/8	0/10	0/9	0/10	9/9
	±	5/8	6/10	8/9	3/10	0/9
	+	3/8	4/10	0/9	5/10	0/9
	++	0/8	0/10	1/9	2/10	0/9
1 %	-	0/8	0/10	0/9	0/10	5/9
	±	4/8	5/10	7/9	0/10	4/9
	+	4/8	4/10	1/9	5/10	0/9
	++	0/8	1/10	1/9	5/10	0/9

The active oxygen elimination agent of this invention has controlled the good allergic inducement reaction so that clearly from this result.

[0049] Next, the example of constituents, such as food, drugs, etc. containing the active oxygen elimination agent obtained in the above-mentioned example, is explained. In addition, especially all the things in which the loadings used for below do not have a notice are the weight sections.

[0050]

[Examples 4-6] The heating dissolution of the A component was carried out at 150 degrees C among the candy table 6, after casting what made B component homogeneity after addition and churning, it cooled and the candy was manufactured [ after cooling at 120 degrees C ].

[0051]

[Table 6]

成 分		配 合 量		
		実施例 4	実施例 5	実施例 6
A	砂 糖 水 鉛	58. 0 30. 0	67. 0 30. 0	67. 0 30. 9
B	クエン酸 実施例 1 の活性酸素消去剤 実施例 2 の活性酸素消去剤 実施例 3 の活性酸素消去剤 香 料	1. 0 10. 0 — — 1. 0	1. 0 — 1. 0 — 1. 0	1. 0 — — 0. 1 1. 0

[0052]

[Example 7] B component which the heating dissolution was carried out [ component ] and carried out the swelling dissolution of the A component of the GUMI table 7 separately at 110 degrees C was added, further, C component was added and it slushed into the mold, and after neglect, it removed from the mold and GUMI was manufactured one whole day and night.

[0053]

[Table 7]

成 分		配 合 量
A	砂 糖	40. 0
	水 餈	45. 0
B	ゼ ラ チ ン	8. 0
C	ク エ ン 酸	2. 0
	実施例 3 の活性酸素消去剤	4. 0
	香 料	1. 0

[0054]

[Example 8] the component of the juice table 8 — good — agitating — a solution — carrying out — sterilization and aseptic — it sealed and juice was manufactured.

[0055]

[Table 8]

成 分		配 合 量
リ ン ゴ 果 汁		98. 0
実施例 1 の活性酸素消去剤		2. 0

[0056]

[Example 9] The component of the hot cake table 9 was often mixed, it roasted with the frying pan which oiled, and the hot cake was created.

[0057]

[Table 9]

成 分		配 合 量
ホットケー キミックス (市販)		240 g
牛 乳		180 ml
全 卵		2 個
実施例 2 の活性酸素消去剤		5 g

[0058]

[Example 10] A component of the granule table 10 was often mixed, and in addition, it corned gradually, carrying out kneading of the B component melted in the ethanol water solution 20 100ml% at this. this — 40 degrees C — 2 day-and-night ventilation desiccation — carrying out — screening — the particle size regulation was carried out and it considered as the granule.

[0059]

[Table 10]

成 分		配 合 量
A	乳 糖	4 5
	デキストラン	4 5
	実施例 1 の活性酸素消去剤	5
B	ヒドロキシプロピルセルロース	5

[0060]

[Example 11] The component of the injections table 11 was dissolved, and it filtered, and sterilized, and into ampul, aseptic was carried out, and it enclosed, and considered as injections.

[0061]

[Table 11]

成 分		配 合 量
塩化ナトリウム		0. 9
実施例 3 の活性酸素消去剤		0. 1
精 製 水		99. 0

[Translation done.]

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## CORRECTION OR AMENDMENT

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[Procedure revision]  
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 [Procedure amendment 1]  
 [Document to be Amended] Specification  
 [Item(s) to be Amended] 0004  
 [Method of Amendment] Modification  
 [Proposed Amendment]  
 [0004] For example, as what is used conventionally, the tocopherol (vitamin E) of lipophilicity, a water-soluble ascorbic acid (vitamin C), etc. are mentioned by the thing of the natural product origin as drugs which have such an operation, and BHT (3, 5-tert-butyl-4-hydroxytoluene), BHA (2(3)-tert-butylhydroxyanisol), etc. are mentioned in a synthetic compound. However, about these drugs, there were problems that an active oxygen elimination operation was not enough and — there arises carcinogenic misgiving — by BHT of a synthetic compound, and BHA.  
 [Procedure amendment 2]  
 [Document to be Amended] Specification  
 [Item(s) to be Amended] 0014  
 [Method of Amendment] Modification  
 [Proposed Amendment]  
 [0014] The constituent containing the active oxygen elimination agent of <2> this inventions  
 The constituent of this invention blends the above-mentioned active oxygen elimination agent according to a conventional method. for example, drugs, food, the charge of makeup, etc. are mentioned.

[Translation done.]

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(54)【発明の名称】活性酸素消去剤及びこれを含有する組成物

## (57)【要約】

【目的】生体内に発生する活性酸素を十分に消去する作用を有し、且つ安全性が高い活性酸素消去剤及びこれを含有する組成物を提供する。

【構成】胡桃殻抽出物を活性酸素消去剤として用いる。また、この活性酸素消去剤を食品、医薬品等の組成物に配合する。

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## 【特許請求の範囲】

【請求項1】 胡桃殻の抽出物からなる活性酸素消去剤。

【請求項2】 前記抽出物が、水、メタノール、エタノール、n-ブロビルアルコール、i-ブロビルアルコール、n-ブチルアルコール、i-ブチルアルコール、sec-ブチルアルコール、t-ブチルアルコール、アセトンから選ばれる1種又は2種以上で抽出されたことを特徴とする請求項1記載の活性酸素消去剤。

【請求項3】 請求項1記載の活性酸素消去剤を含有する組成物。 10

## 【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、活性酸素消去剤及びこれを含有する組成物に関し、詳しくは、胡桃殻の抽出物からなる活性酸素消去剤及びこの活性酸素消去剤を含有する組成物に関する。

【0002】

【従来の技術】一般的に、活性酸素が生体へ及ぼす影響としては、コラーゲン線維の架橋や、DNA螺旋の部分開裂、連鎖的ラジカルの発生による組織の損傷が挙げられ、その結果としてシワや彈力消失といった皮膚や生体の老化、気管支喘息等のアレルギー反応の惹起とヒスタミン放出による炎症の惹起、虚血性疾患のひとつである心筋梗塞における平滑筋の損傷、肝臓障害などの疾患の悪化、また、脳組織の破壊による痴呆の誘発などが引き起こされることが知られている。更に、詳細な原因、機構は不明であるがリューマチの発症にも活性酸素が関与していることも公知の事実である。

【0003】従って、生体内において活性酸素の発生を抑制することは、これらの疾患を治療あるいは予防する点で非常に重要なことであり、このため、従来より生体内に発生した活性酸素を消去する作用を有する薬剤の探索研究が広く行われてきた。

【0004】例えば、このような作用を有する薬剤として、従来より用いられているものとしては、天然物由來のものでは、脂溶性のトコフェロール（ビタミンE）、水溶性のアスコルビン酸（ビタミンC）等が挙げられ、合成化合物では、BHT（3, 5-tert-ブチル-4-ヒドロキシトルエン）、BHA（2(3)-tert-ブチル-ヒドロキシアニリール）等が挙げられる。しかし、これらの薬剤に関しては、活性酸素消去作用が十分でなく、また合成化合物のBHT、BHAでは、発ガン性の疑いが持たれている等の問題があった。

【0005】また、最近では、十分な薬効と安全性を求めて、生葉抽出物から活性酸素消去作用を有する薬剤を得ようという試みも數多くなされている。例えば、特開昭60-224629号、特開昭61-24522号、特開平2-193930号、特開平2-243632号、特開平2-264727号、特開平3-15362 20

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9号、特開平3-221587号、特開平4-69343号、特開平4-202138号、特開平4-247010号など、これらは全て生葉由来物の活性酸素消去作用を利用したものである。しかし、これらの生葉抽出物では、安全性には問題がないものの、活性酸素消去作用の点から言えば、未だ十分なもののは得られていなかった。

【0006】更に、酵素のひとつスーパー・オキサイドデスマニューターゼ（SOD）を投与することにより、生体内に発生する活性酸素を消去する試みもなされてきているが、SODは、タンパク質であるため、その入手が困難であるばかりでなく、消化されてしまうが故に、経口投与は不可能であり、また、注射による投与でも血中半減期が短く満足の行くものではなかった。

【0007】一方、胡桃の殻については、その粉碎物がスクラップ剤として有用である知見や、その抽出エキスが、皮膚外用剤として保湿性に優れ有用である知見が知られている。しかし、この胡桃殻の抽出エキスが、活性酸素消去作用を有することは知られておらず、また、これを医薬品、食品等に含有させて、上述したような様々な疾患の予防や治療、老化の防止、改善に用いるという試みはされていなかった。

【0008】

【発明が解決しようとする課題】本発明は、上記観点からなされたものであり、生体内に発生する活性酸素を十分に消去する作用を有し、且つ安全性が高い活性酸素消去剤及びこれを含有する組成物を提供することを課題とする。

【0009】

【課題を解決するための手段】本発明者らは、上記課題を解決するために、活性酸素消去作用を指標として各種物質をスクリーニングする中で、活性酸素により劣化をうけやすい不飽和油脂を殻の内部に含む胡桃の実が、内部の不飽和油脂を安定に保てるのは、外の殻に何らかの活性酸素に対する防御機構が存在するためではないかと推論し、活性酸素消去剤のスクリーニングに胡桃殻抽出物をかけたところ、この胡桃殻抽出成分に優れた活性酸素消去作用を有する成分が存在することを見出し、本発明を完成するに至った。

【0010】すなわち、本発明は胡桃殻の抽出物からなる活性酸素消去剤及びこれを含有する組成物に関する。以下、本発明を詳細に説明する。

【0011】&lt;1&gt;本発明の活性酸素消去剤

本発明の活性酸素消去剤は、胡桃殻の抽出物からなる。本発明に用いる胡桃殻とは、一般的に知られている、クルミ科植物の果実の殻であり、例えば、オニグルミ、マンシュウグルミ、ウォールナットなどの胡桃殻が挙げられる。

【0012】上記胡桃殻は、活性酸素消去作用を有する成分を含んでおり、抽出により前記成分を含む抽出物を

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取り出して、本発明の活性酸素消去剤として用いる。胡桃殻の抽出処理は、連続式、バッチ式等の方法で、常法により冷浸または温浸にて任意の時間行う。例えば、胡桃殻を細かく粉碎し、抽出溶媒に、室温で1～3日間、または抽出溶媒の沸騰温度で1時間～5時間、浸漬し抽出を行う。その後、抽出液から抽出残渣を除いて、減圧または限外濾過を行い抽出物を濃縮する。さらに、必要に応じて有機溶媒を完全に留去して乾固するかまたは凍結乾燥する。

【0013】このような抽出に用いる溶媒としては、水や各種有機溶媒が挙げられるが、本発明においては特に、水、メタノール、エタノール、n-ブロビルアルコール、i-ブロビルアルコール、n-ブチルアルコール、i-ブチルアルコール、sec-ブチルアルコール、t-ブチルアルコール、アセトンから選ばれる1種または2種以上が好ましい。

【0014】<2>本発明の活性酸素消去剤を含有する組成物

本発明の組成物は、上記活性酸素消去剤を、常法に従って配合したものであり、例えば、医薬品、食品等が挙げられる。

【0015】本発明の活性酸素消去剤を医薬品として製剤化する場合、剤型は特に限定されないが、注射剤、散剤、顆粒剤、錠剤、カプセル剤、液剤など通常用いられている各種製剤へ、賦形剤、結合剤、崩壊剤、滑沢剤、着色剤、矯味剤、矯臭剤、增量剤、被覆剤などの医薬品で通常用いられる任意成分とともに、通常の方法に従って剤型化できる。

【0016】上記医薬品の投与量に関しては、疾患の種類、症状、患者の年齢、体重などにより異なるが、成人1人1日あたり、胡桃殻の抽出物の量として10mg～1000mgを1回ないし数回に分けて経口投与するか、5mg～500mgを注射で投与するのが適当である。注射剤の投与方法としては、静脈内投与、動脈内投与、門脈内投与、腹腔内投与、筋肉内投与、皮下投与等が挙げられる。

【0017】本発明の活性酸素消去剤を食品に配合する場合、特に留意することなく、種々の食品へ、食品で通常用いられている任意成分とともに配合できる。例示をすれば、キャンディーやグミ、ゼリーといったお菓子類やジュースのようなドリンク類、パンなどの主食等が挙げられる。配合量は、食品の種類により異なるが、食品の味を損なわずに、且つ十分な活性酸素消去効果を得るために、0.1～10重量%が好ましい。

【0018】なお、胡桃殻の抽出物は、胡桃が可食果実であることから安全性に優れていることが期待できる。

【0019】

【作用】本発明の活性酸素消去剤及びこれを含有する組成物は、その有効成分である胡桃殻抽出物の優れた活性酸素消去作用により、上述したように活性酸素が関与し

ているとされる、炎症、老人性痴呆、心筋梗塞などの虚血性疾患、あるいはアレルギー性疾患、肝臓障害、リューマチなど様々な疾病的治療や皮膚などの生体老化の改善に対して有効に働くものである。

【0020】また、本発明の活性酸素消去剤及びこれを含有する組成物は、上記疾病や生体老化の予防のためにも有効に使用できる。これは、活性酸素消去作用を有する成分を、あらかじめ生体内に存在させることにより、生体内で発生した活性酸素を素早く消去し、無毒化することができるためである。

【0021】

【実施例】以下に、本発明の実施例を説明する。はじめに、本発明の活性酸素消去剤の実施例を説明する。

【0022】

【実施例1】オニグルミの胡桃殻500gを細かく粉碎し、これに5lの水を加え、105℃で2時間加熱攪拌した後、濾過して残渣を取り除き、得られた濾液を2昼夜かけて凍結乾燥して、オニグルミの胡桃殻抽出物を4.9gの褐色粉末として得た。これを、そのまま活性酸素消去剤とした。

【0023】

【実施例2】マンシュウグルミの胡桃殻500gを細かく粉碎し、これにメタノールとn-ブチルアルコールの等量混合液5lを加え、攪拌、加熱、還流を2時間行った後、濾過して残渣を取り除き、得られた濾液を減圧濃縮して、マンシュウグルミの胡桃殻抽出物を5.3gを粘稠性液体として得た。これを、そのまま活性酸素消去剤とした。

【0024】

【実施例3】ウォールナツの胡桃殻500gを細かく粉碎し、これに50%アセトン水溶液5lを加え、攪拌、加熱、還流を2時間行った後、濾過して残渣を取り除き、得られた濾液を減圧濃縮した。更に、この濃縮物を48時間かけて凍結乾燥処理し、ウォールナツの胡桃殻抽出物を5.1gのアモルファスとして得た。これを、そのまま活性酸素消去剤とした。

【0025】<活性酸素消去剤の評価>上記各実施例で得られた活性酸素消去剤について、安全性、活性酸素消去作用、及び老化、肝臓障害、アレルギー疾患に対する効果に関する評価を行った。

【0026】(1) 急性毒性試験

1群2匹づつの5週齢ICR雄性マウス（体重25～30g）の腹腔内に、実施例1で得られた活性酸素消去剤を生理食塩水に溶解したものを、それぞれ500mg/kg、1000mg/kg、2000mg/kgの割合で投与し、14日後に生死の判定を行った。その結果、前記何れの投与量においてもマウスは生存し、LD<sub>50</sub>値は2000mg/kg以上であることが確認された。このことより本発明の活性酸素消去剤が安全性に優れることが明白である。

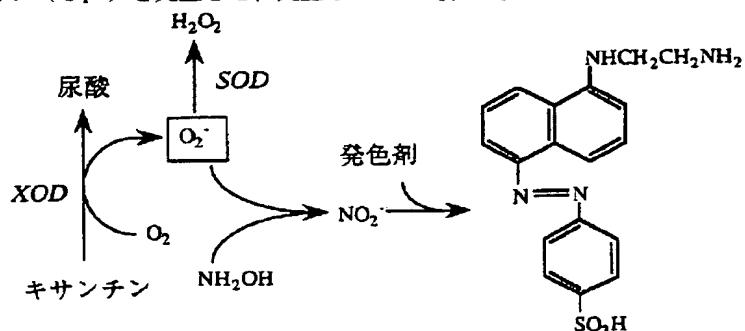
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〔0027〕(2) 活性酸素消去作用の測定(インピトロ)  
 化1に示す反応式に基づき、キサンチン-キサンチンオキシダーゼ(XOD)系により活性酸素のひとつであるスーパーオキシドアニオン( $O_2^-$ )を発生させ、発生し\*

\* たO<sub>2</sub><sup>-</sup>の生成率を亜硝酸法により測定し、この値をキサンチンオキシダーゼ阻害活性値で補正して活性酸素消去作用値を求めた。

[0028]

【化 1】



〔0029〕上記各実施例で得られた活性酸素消去剤を500μg/mlの割合で含有する活性酸素消去剤水溶液0.1mlを、65mMリン酸2水素カリウム、35mMホウ酸ナトリウム、0.5mMEDTA2ナトリウム水溶液（以下、緩衝液Aという）0.2ml、0.5mMキサンチン溶液0.2ml、10mMヒドロキシルアミン塩酸塩水溶液0.1ml、純水0.2mlの混合液に、加えてよく攪拌し試験液とした。同様にして、活性酸素消去剤の代わりに純水0.1mlを用いたコントロールの溶液を作製した。

〔0030〕上記各試験液及びコントロール溶液に、キサンチンオキシダーゼを $1\text{ }\mu\text{l}/\text{ml}$ 濃度で含有する緩衝液Aを $0.\text{2 ml}$ 加えて攪拌した後、 $37^\circ\text{C}$ で30分インキュベーションした。プランクとして、上記と同様に調整された試験液及びコントロール溶液に、キサンチンオキシダーゼを含まない緩衝液Aを $0.\text{2 ml}$ 加え、上記と同様に処理した溶液を用意した。

〔0031〕このようにして得られた各溶液のそれぞれ※

※に、 $30\mu\text{M}$  MN-1-ナフチルエチレンジアミン塩酸塩、 $3\text{mM}$  スルファニル酸、 $25\%$  水酢酸混液 $2\text{mL}$ を加え、 $30$ 分間室温で放置した後、各溶液について、 $520\text{nm}$ での吸光度で活性酸素の発生量を、 $295\text{nm}$ の吸光度で尿酸の発生量を測定した。

【0032】得られた値を用いて、以下の式に基づき、活性酸素消去活性値を算出した。結果を表2に示す。

〔0033〕<活性酸素消去活性を求める式>

$$\text{活性酸素発生率} = [(A_{550-3} - A_{550-4}) / (A_{550-1} - A_{550-2})] \times 100$$

$$\text{尿酸生成率} = [ (A_{295-3} - A_{295-4}) / (A_{295-1} - A_{295-2}) ] \times 100$$

活性酸素消去活性 = 100 - (活性酸素発生率 / 尿酸生成率) × 100

但し、式中の記号は、表1に示す条件で調整された各溶液の吸光度の値とする。

[0034]

[表 1]

測定波長 (nm)		キサンチンオキシダーゼ	
		存在下	非存在下
550 (活性酸素量)	コントロール 試験液	A <sub>550-1</sub> A <sub>550-3</sub>	A <sub>550-2</sub> A <sub>550-4</sub>
295 (尿酸量)	コントロール 試験液	A <sub>295-1</sub> A <sub>295-3</sub>	A <sub>295-2</sub> A <sub>295-4</sub>

(00351)

【表2】

	活性酸素消去活性値 (%)
実施例 1 の活性酸素消去剤	67.1
実施例 2 の活性酸素消去剤	66.2
実施例 3 の活性酸素消去剤	67.5

以上の結果から、本発明の活性酸素消去剤が、優れた活性酸素消去作用を有することは明らかである。

【0036】(3) 活性酸素消去作用の測定（インピボ）

35週齢 ICR 系MCH 雄性マウス（体重30～40g）から採血を行った後、このマウスに実施例1で得られた活性酸素消去剤を、1000mg/kgの割合で経口投与した。投与30分後、2時間後、5時間後に採血を行った。上記各条件で採血した血液から遠心分離により血清を取り出し、これを、緩衝液Aで10倍に希釈して、上記(2)の試験と同様の方法で活性酸素消去活性を測定した。結果を表3に示す。

【0037】

【表3】

	活性酸素消去活性値 (%)
投与前	47.8 ± 15.4
投与30分後	62.9 ± 10.9
2時間後	49.6 ± 7.6
5時間後	58.4 ± 4.5

この結果から、本発明の活性酸素消去剤は、経口投与により速やかに血中に移行し、長時間その効果を保つことが明白である。

【0038】(4) 老化、肝障害に対する効果の検討

10 5週齢ウィスター系雌性ラット40匹を体重にばらつきのない様に4群に分け、1群には通常の固形飼料(F, 飼料、船橋農場製)を、他の3群にはそれぞれ、各実施例の活性酸素消去剤を前記固形飼料に1重量%の配合したもの摂取させて24ヶ月飼育した。なお、実験中、ラットには、固形飼料及び水を自由に摂取できるようにした。

【0039】24ヶ月飼育後、各群のラットから血液を採取した後、屠殺した。その後、各群のラットについて老化の評価指標として散在性脱毛、表皮下の結合組織の膨化断裂、脂腺、汗腺の消失に関して出現の有無を観察した。

【0040】更に、これらのラットを解剖して肝臓を摘出し、肉眼観察の上病理標本として顕微鏡下観察することにより肝障害に関する評価を行った。また、生体内に活性酸素が発生すると、体内の不飽和脂肪酸と容易に反応して過酸化脂質を生じるが、このようにして体内各部（血清中、脳中、肝臓中）に生じた過酸化脂質の量をTBA法で測定することにより、各器官における活性酸素消去効果の評価を行った。

【0041】結果を、過酸化脂質量については10匹の平均値として、その他の評価項目については出現匹数として、表4に示す。

【0042】

【表4】

		実施例1	実施例2	実施例3	コントロール
過酸化脂質量	血清中	11	10	10	18
	脳中	24	25	23	27
	肝臓中	29	29	27	36
<老化の評価>					
散在性脱毛		0	0	0	3
表皮下の結合組織の膨化断裂		0	0	0	4
脂腺、汗腺の消失		0	0	0	2
<肝障害の評価>					
肝臓への脂肪沈着		0	0	0	6
肝臓小葉への炎症細胞の浸潤		0	0	0	4
萎縮肝細胞		0	0	0	2

本発明の活性酸素消去剤は、体内の各器官において、活性酸素を消去することで過酸化脂質の生成をよく抑制し、生体の老化を防ぎ、且つ肝臓の障害を防いでいることが明らかである。

【0043】(5)アレルギー疾患に対する効果の検討クリーチャンのモルモットマキシマイゼーションテスト法に準じて、感作物質であるシンナムアルデヒドを用いて、アレルギー性の惹起反応に対する評価を行った。

【0044】1群8~10匹づつのモルモットの2群(このうち1群はコントロール群)には通常の固形飼料(F<sub>1</sub>飼料、船橋農場製)と水を、他の3群にはそれぞれ、各実施例の活性酸素消去剤を前記固形飼料に1重量%の配合したものと水を、自由に摂取させて飼育しながら以下の実験を行った。

【0045】コントロール群のモルモットを除いた、上記各群のモルモットに、2日おきに4回、1%シンナムアルデヒド流動パラフィン溶液とフロイントの完全アジュバントの等量混合液、1%シンナムアルデヒド流動パラフィン溶液及びフロイントの完全アジュバントを、各

0.05mlづつ背部の2ヶ所に皮内注射した。更に、注射開始日より注射終了日までの期間、上記注射部位に、1%シンナムアルデヒド流動パラフィン溶液を絆創膏のバット部に塗布したものをクローズドパッチして、経皮投与も同時に行なった。

【0046】注射及びクローズドパッチ終了日の2週間後、すべてのモルモットの背部を剃毛し、0.01%、0.05%、0.1%、0.5%、1%濃度の各シンナムアルデヒド流動パラフィン溶液を、上記と同様にクローズドパッチする方法で、24時間経皮投与して、惹起反応を見た。評価の基準は、以下に示す日本皮膚科学会・本邦パッチテスト基準を用いた。結果を表5に示す。

【0047】- : 無反応

± : 疑陽性反応

+ : 陽性反応

++ : 浮腫を伴う反応

【0048】

【表5】

		実施例1	実施例2	実施例3	通常飼料	コントロール群
0.01%	-	4/8	4/10	5/9	3/10	9/9
	±	4/8	6/10	4/9	4/10	0/9
	+	0/8	0/10	0/9	3/10	0/9
	++	0/8	0/10	0/9	0/10	0/9
0.05%	-	4/8	4/10	5/9	2/10	9/9
	±	4/8	6/10	4/9	3/10	0/9
	+	0/8	0/10	0/9	5/10	0/9
	++	0/8	0/10	0/9	0/10	0/9
0.1%	-	2/8	2/10	3/9	0/10	9/9
	±	4/8	5/10	6/9	4/10	0/9
	+	2/8	3/10	0/9	5/10	0/9
	++	0/8	0/10	0/9	1/10	0/9
0.5%	-	0/8	0/10	0/9	0/10	9/9
	±	5/8	6/10	8/9	3/10	0/9
	+	3/8	4/10	0/9	5/10	0/9
	++	0/8	0/10	1/9	2/10	0/9
1%	-	0/8	0/10	0/9	0/10	5/9
	±	4/8	5/10	7/9	0/10	4/9
	+	4/8	4/10	1/9	5/10	0/9
	++	0/8	1/10	1/9	5/10	0/9

この結果から明らかなように、本発明の活性酸素消去剤は、よくアレルギー性の惹起反応を抑制している。  
【0049】次に、上記実施例で得られた、活性酸素消去剤を含有する、食品、医薬品等の組成物の実施例について説明する。なお、以下に用いる配合量は、特にことわりのないものは、すべて重量部である。

【0050】

## \* 【実施例4～6】 キャンディー

30 表6中、A成分を150℃で加熱溶解し、120℃に冷却後、B成分を添加、攪拌後、均一としたものを成型後、冷却してキャンディーを製造した。

【0051】

【表6】

\*

成 分		配 合 量		
		実施例4	実施例5	実施例6
A	砂 糖 水 鮎	58.0 30.0	67.0 30.0	67.0 30.9
B	クエン酸 実施例1の活性酸素消去剤 実施例2の活性酸素消去剤 実施例3の活性酸素消去剤 香 料	1.0 10.0 — — 1.0	1.0 — 1.0 — 1.0	1.0 — — 0.1 1.0

【0052】

50 【実施例7】 グミ

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表7のA成分を110°Cで加熱溶解し、別途膨潤溶解させたB成分を添加し、更に、C成分を添加し、型に流し込み、一昼夜放置後、型からはずしてグミを製造した。

【0053】

【表7】

成 分		配 合 量
A	砂 糖	40.0
	水 鉛	45.0
B	ゼ ラ チ ン	8.0
C	ク エ ン 酸 実施例3の活性酸素消去剤 香 料	2.0 4.0 1.0

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\* 表8の成分をよく摂拌して溶液とし、滅菌、無菌充填、密閉してジュースを製造した。

【0055】

【表8】

成 分	配 合 量
リンゴ果汁 実施例1の活性酸素消去剤	98.0 2.0

【0056】

【実施例9】 ホットケーキ

表9の成分をよく混ぜ合わせ、油を引いたフライパンで焼き上げホットケーキを作成した。

【0057】

【表9】

【0054】

【実施例8】 ジュース

\*

成 分	配 合 量
ホットケーキミックス(市販)	240g
牛 乳	180ml
全 卵	2個
実施例2の活性酸素消去剤	5g

【0058】

\* 徐々に加え造粒した。これを40°Cで2昼夜送風乾燥し、篩過、整粒して顆粒剤とした。

【実施例10】 顆粒剤

表10のA成分をよく混合し、これに100mlの20~30%エタノール水溶液に溶かしたB成分を練合させながら※

【0059】

【表10】

成 分		配 合 量
A	乳 糖	45
	デキストラン	45
	実施例1の活性酸素消去剤	5
B	ヒドロキシプロビルセルロース	5

【0060】

充填して封入し、注射剤とした。

【実施例11】 注射剤

【0061】

表11の成分を溶解、濾過、滅菌し、アンプル中へ無菌

【表11】

成 分	配 合 量
塩化ナトリウム	0. 9
実施例3の活性酸素消去剤	0. 1
精 製 水	99. 0

【0062】

【発明の効果】本発明の活性酸素消去剤およびこれを含  
有する組成物は、安全性が高く、優れた活性酸素消去作 10

用を有するので、活性酸素が関与するアレルギー疾患、  
肝障害の予防と治療、生体老化の防止に有効である。

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【手続補正書】

【提出日】平成7年5月17日

【手続補正1】

【補正対象書類名】明細書

【補正対象項目名】0004

【補正方法】変更

【補正内容】

【0004】例えば、このような作用を有する薬剤として、従来より用いられているものとしては、天然物由來のものでは、脂溶性のトコフェロール(ビタミンE)、水溶性のアスコルビン酸(ビタミンC)等が挙げられ、合成化合物では、BHT(3,5-tert-ブチル-4-ヒドロキシトルエン)、BHA(2(3)-tert-ブチル-ヒドロキシアニソール)等が挙げられる。

しかし、これらの薬剤に関しては、活性酸素消去作用が十分でなく、また合成化合物のBHT、BHAでは、発ガン性の疑いが持たれている等の問題があった。

【手続補正2】

【補正対象書類名】明細書

【補正対象項目名】0014

【補正方法】変更

【補正内容】

【0014】<2>本発明の活性酸素消去剤を含有する組成物

本発明の組成物は、上記活性酸素消去剤を、常法に従って配合したものであり、例えば、医薬品、食品、化粧料等が挙げられる。